General

Guideline Title

Rivaroxaban for preventing adverse outcomes after acute management of acute coronary syndrome.

Bibliographic Source(s)

National Institute for Health and Care Excellence (NICE). Rivaroxaban for preventing adverse outcomes after acute management of acute coronary syndrome. London (UK): National Institute for Health and Care Excellence (NICE); 2015 Mar. 43 p. (Technology appraisal guidance; no. 335).

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

Rivaroxaban is recommended as an option within its marketing authorisation, in combination with aspirin plus clopidogrel or aspirin alone, for preventing atherothrombotic events in people who have had an acute coronary syndrome (ACS) with elevated cardiac biomarkers.

Clinicians should carefully assess the person's risk of bleeding before treatment with rivaroxaban is started. The decision to start treatment should be made after an informed discussion between the clinician and the patient about the benefits and risks of rivaroxaban in combination with aspirin plus clopidogrel or with aspirin alone, compared with aspirin plus clopidogrel or aspirin alone.

A decision on continuation of treatment should be taken no later than 12 months after starting treatment. Clinicians should regularly reassess the relative benefits and risks of continuing treatment with rivaroxaban and discuss them with the patient.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Atherothrombotic events after acute coronary syndrome (ACS; ST-segment elevation myocardial infarction [STEMI], non-ST-segment elevation myocardial infarction [NSTEMI], or unstable angina [UA]) with elevated cardiac biomarkers

Guideline Category

Assessment of Therapeutic Effectiveness

Prevention

Treatment

Clinical Specialty

Cardiology

Emergency Medicine

Family Practice

Internal Medicine

Preventive Medicine

Intended Users

Advanced Practice Nurses

Hospitals

Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To assess the clinical effectiveness and cost-effectiveness of rivaroxaban for preventing adverse outcomes after acute management of acute coronary syndrome (ACS)

Target Population

Adults after acute management of an acute coronary syndrome (ACS) with elevated cardiac biomarkers

Interventions and Practices Considered

Rivaroxaban in combination with aspirin plus clopidogrel or aspirin alone

Major Outcomes Considered

- Clinical effectiveness
  - Death from any cause
  - Non-fatal cardiovascular events

    - Incidence of revascularisation procedures
    - Adverse effects of treatment (including bleeding events)
    - Health-related quality of life
- Cost effectiveness

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Searches of Unpublished Data

Description of Methods Used to Collect/Select the Evidence

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Care Excellence (NICE) commissioned an independent academic centre to perform an assessment of the manufacturer's submission (MS) on the technology considered in this appraisal and prepare an Evidence Review Group (ERG) report. The ERG report for this appraisal was prepared by the School of Health and Related Research (ScHARR), the University of Sheffield (see the "Availability of Companion Documents" field).

Clinical Effectiveness

Critique of the Methods of Review(s)

Searches

The searches undertaken by the manufacturer to identify all relevant randomised controlled trials (RCTs) were conducted in March 2014. The search strategy utilised appropriate free text and medical subject heading terms to identify the condition (acute coronary syndrome [ACS]), the intervention (rivaroxaban) and the type of evidence (RCTs). Searches were further restricted to human and English language publications. Although the strategy is simple and effective, justification for adapting the published methodological RCT search filter (that was originally developed by the Scottish Intercollegiate Guidelines Network) was lacking. Several electronic bibliographic databases (MEDLINE, MEDLINE in Process, EMBASE, and the Cochrane Library) were searched from inception. Although research registers such as ClinicalTrials.gov and the International Standard Randomised Controlled Trial Number Register were not searched, three conference proceedings (American Heart Association Scientific Sessions, European Society of Cardiology and American College of Cardiology) were reviewed for relevant abstracts presented at meetings held in 2012 and 2013. Supplementary searches such as scanning of bibliographies of included studies, existing systematic reviews, manufacturer's database of trial protocols, clinical study reports and correspondence with regulatory bodies were also undertaken. The number of hits following a repeat of the electronic database search strategies for the identification of relevant rivaroxaban intervention studies on 28 July 2014 (see Section 6.1 in the MS) by the ERG, show numbers to be consistent with those reported in the MS. Whilst the ERG considers the search strategies to be comprehensive to retrieve important citations relating to all eligible studies of which the ERG and its clinical advisors are aware of, restricting the searches by English language can lead to publication bias.

Inclusion Criteria

The MS describes an appropriate method of identifying and screening references for inclusion in the systematic review of rivaroxaban for the prevention of atherothrombotic events in adult patients after an ACS with elevated cardiac biomarkers. Two independent reviewers applied pre-specified inclusion and exclusion criteria (via a two-stage sifting process) to citations identified by the searches. Any differences in selection were resolved through discussion with a third reviewer. A summary of the inclusion and exclusion criteria, as reported in the MS for the systematic review of rivaroxaban is summarised in Table 3 in the ERG report.

The specified inclusion and exclusion criteria were appropriate and generally reflect the information given in the decision problem.

Refer to the ERG report for additional details on the clinical effectiveness searches, including the search strategies used.

Cost-effectiveness

ERG Comment on Manufacturer's Review of Cost-effectiveness Evidence

Description of Manufacturers Search Strategy and Comment on Whether the Search Strategy Was Appropriate

The manufacturer performed a literature search to identify published cost-effectiveness analyses of interventions for the secondary prevention of ACS events. The search was performed in March 2014 in several electronic bibliographic databases: MEDLINE, MEDLINE in Process, EMBASE and the Cochrane Library. Additional sources included UK Health Technology Assessment (HTA) Web sites (NICE and the Scottish Medicines Consortium) and conference proceedings of the American Heart Association scientific sessions (2012-13), European Society of Cardiology (2013), American College of Cardiology (2013) and the International Society for Pharmacoeconomics and Outcomes Research (2013). Appropriate filters were used to retrieve cost-effectiveness studies and details of searches for conference proceedings and of UK HTA Web sites were clearly reported.

Inclusion/Exclusion Criteria Used in the Study Selection and Comment on Whether They Were Appropriate

The inclusion/exclusion criteria used in the manufacturer's study selection are provided in Table 10 in the ERG report. The search strategy was broad and covered many relevant interventions for ACS. Cost-effectiveness studies of ticagrelor and prasugrel were included in the systematic review even though they were not included in the final scope issued by NICE. This was because cost-effectiveness models for these interventions could provide useful information on costs and utilities of the health states in a *de novo* model, if developing one was required.

The ERG had some concerns about the country specific inclusion/exclusion criteria, as no rationale was provided for only identifying studies from the USA, Canada, United Kingdom, Germany, France, Italy and Spain. However, given the values used in the model it is unlikely that the country specific exclusion criteria lead to the exclusion of studies which contained parameters of greater relevance to the decision problem.

Refer to the ERG report for additional details on the cost-effectiveness searches, including the search strategies used.

Number of Source Documents

Clinical Effectiveness

Of the 562 citations identified from the manufacturer's submission (MS), two randomised controlled trials (RCTs) (representing 21 citations) met the inclusion criteria (the Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome–Thrombolysis in Myocardial Infarction 46 [ATLAS ACS-TIMI 46] study and the ATLAS ACS 2-TIMI 51 trial).

Cost-effectiveness

- The systematic review identified a total of 59 records, 46 of which were unique mathematical models. Of the 46 identified mathematical models, 8 were presented in conference abstract form. The manufacturer identified no studies which had evaluated the cost-effectiveness of rivaroxaban plus aspirin with or without clopidogrel compared to aspirin with or without clopidogrel for the secondary prevention of acute coronary syndrome (ACS).
- The manufacturer presented an economic model.

Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Care Excellence (NICE) commissioned an independent academic centre to perform an assessment of the manufacturer's submission (MS) on the technology considered in this appraisal and prepare an Evidence Review Group (ERG) report. The ERG report for this appraisal was prepared by the School of Health and Related Research (ScHARR), the University of Sheffield (see the "Availability of Companion Documents" field).

Clinical Effectiveness

Critique of Data Extraction

The data extracted and presented in the MS clinical section appear appropriate and comprehensive. As noted in the manufacturer's response to a clarification question, data extraction was performed by one researcher and checked by a second. Any disagreements were resolved by consensus and if necessary, a third reviewer was consulted.

Quality Assessment

The validity assessment tool used to appraise the included studies in the MS was based on the minimum criteria for assessment of risk of bias in randomised controlled trials (RCTs), as suggested by the Centre for Reviews and Dissemination. As noted in the manufacturer's response to a clarification question, methodological quality assessment of included studies was performed by one researcher and checked by a second. The ERG acknowledges that the validity assessment tool used in the MS was appropriate.

Evidence Synthesis

The manufacturer did not undertake a formal meta-analysis as only one rivaroxaban RCT study was considered relevant to the submission. As a result, the manufacturer undertook a narrative synthesis of the evidence; however, no explicit details were provided on how this approach was undertaken. Ideally, a narrative synthesis approach should be pre-specified, justified, rigorous (i.e., describe results without being selective or emphasising some finding over others) and transparent to reduce potential bias. Despite the lack of transparency, the ERG acknowledges that the narrative synthesis approach undertaken by the manufacturer was acceptable.

Refer to Section 4 in the ERG report for additional information on clinical effectiveness analysis.

Cost-effectiveness

As no cost-effectiveness studies comparing rivaroxaban plus aspirin with or without clopidogrel to aspirin with or without clopidogrel in the secondary prevention of acute coronary syndrome (ACS) were identified by the manufacturer, a *de novo* model was constructed.

The Model Structure

The manufacturer submitted a state transition cohort model written in Microsoft Excel (Microsoft Corporation, Redmond, Washington). The model used a time horizon of 40 years that was divided into two periods: an observation period which was intended to replicate the duration of the trial data and an extrapolation period. The extrapolation period started after 96 weeks and had a cycle length of 6 months. In the observation period the initial two cycles had a cycle length of 4 and 8 weeks respectively and the remaining cycles used a cycle length of 12 weeks. In the manufacturer's initial submission 96 weeks was assumed to last two years instead of 104 weeks. This discrepancy was introduced by assuming that cycle lengths of 12 weeks represented a quarter of a year (13 weeks).

In the manufacturer's response to a clarification question, it was established that these time cycles were chosen so that the model cycles matched the data collection points in the trial. It is unclear to the ERG why this was done, as in the manufacturer’s base case Weibull curves were used to interpolate the data. Therefore the manufacturer could obtain transition probabilities between any two time points that they chose, not just the data collection points in the trial data.

In the base case, costs and quality-adjusted life-years (QALYs) are both discounted at a rate of 3.5% as recommended by NICE. Half cycle correction was performed on the Markov trace. The model structure is presented in Figure 5 of the ERG report,

The Health States within the Model

The model consisted of a number of health states corresponding to whether no further ACS event occurred or whether the patient suffered an ACS event. The ACS events considered in the model were: myocardial infarction, ischaemic stroke, haemorrhagic stroke or intracranial haemorrhage; a bleeding event measured on the thrombolysis in myocardial infarction (TIMI) scale; and revascularisation. These ACS events fell into two broad categories: those with longer term implications for the relative risks of developing further conditions, utility and costs; and those

deemed to be transient events where the impacts were limited to one model cycle.

Refer to Section 5 in the ERG report for additional details about the economic model.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Considerations

Technology appraisal recommendations are based on a review of clinical and economic evidence.

Technology Appraisal Process

The National Institute for Health and Care Excellence (NICE) invites 'consultee' and 'commentator' organisations to take part in the appraisal process. Consultee organisations include national groups representing patients and carers, the bodies representing health professionals, and the manufacturers of the technology under review. Consultees are invited to submit evidence during the appraisal and to comment on the appraisal documents.

Commentator organisations include manufacturers of the products with which the technology is being compared, the National Health Service (NHS) Quality Improvement Scotland and research groups working in the area. They can comment on the evidence and other documents but are not asked to submit evidence themselves.

NICE then commissions an independent academic centre to review published evidence on the technology and prepare an 'assessment report'. Consultees and commentators are invited to comment on the report. The assessment report and the comments on it are then drawn together in a document called the evaluation report.

An independent Appraisal Committee then considers the evaluation report. It holds a meeting where it hears direct, spoken evidence from nominated clinical experts, patients and carers. The Committee uses all the evidence to make its first recommendations, in a document called the 'appraisal consultation document' (ACD). NICE sends all the consultees and commentators a copy of this document and posts it on the NICE Web site. Further comments are invited from everyone taking part.

When the Committee meets again it considers any comments submitted on the ACD; then it prepares its final recommendations in a document called the 'final appraisal determination' (FAD). This is submitted to NICE for approval.

Consultees have a chance to appeal against the final recommendations in the FAD. If there are no appeals, the final recommendations become the basis of the guidance that NICE issues.

Who Is on the Appraisal Committee?

NICE technology appraisal recommendations are prepared by an independent committee. This includes health professionals working in the NHS and people who are familiar with the issues affecting patients and carers. Although the Appraisal Committee seeks the views of organisations representing health professionals, patients, carers, manufacturers and government, its advice is independent of any vested interests.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

Summary of Appraisal Committee's Key Conclusions

Availability and Nature of Evidence

The Committee considered the company's economic model and the review and exploratory sensitivity analyses performed by the Evidence Review

Group (ERG).

Uncertainties Around and Plausibility of Assumptions and Inputs in the Economic Model

The Committee was aware of the ERG's concerns about the structure of the company's economic model and, in particular, that the model is relatively inflexible. This meant that the ERG could not carry out all the exploratory analyses that it deemed potentially relevant. These included amendments to the hazard ratio for fatal bleeds and adjusting for the possibility of informative censoring.

Incorporation of Health-related Quality-of-Life Benefits and Utility Values. Have Any Potential Significant and Substantial Health-related Benefits Been Identified That Were Not Included in the Economic Model, and How Have They Been Considered?

Not applicable. The Committee did not draw any specific conclusions about the health-related quality of life benefits and utility values.

Are There Specific Groups of People for Whom the Technology Is Particularly Cost Effective?

The Committee did not identify specific groups of people for whom the technology is particularly cost effective.

What Are the Key Drivers of Cost-effectiveness?

Not applicable. The Committee did not draw any specific conclusions about the key drivers of cost effectiveness.

Most Likely Cost-effectiveness Estimate (Given as an Incremental Cost-Effectiveness Ratio [ICER])

The Committee noted that the company's base case ICER was £6203 per quality-adjusted life year (QALY) gained, and the ERG's preferred base case estimate was £5622 per QALY gained. It accepted that there is uncertainty about the validity of the results based on ATLAS-ACS 2-TIMI 51 because of the risk of bias resulting from missing data and informative censoring. However, the Committee considered that the ICERs presented were all within the range that could be considered cost effective and that the results of the ERG's exploratory sensitivity and scenario analyses suggested that the ICER was unlikely to increase to the extent that it would become unacceptable.

Method of Guideline Validation

External Peer Review

Description of Method of Guideline Validation

Consultee organisations from the following groups were invited to comment on the draft scope, Assessment Report and the Appraisal Consultation Document (ACD) and were provided with the opportunity to appeal against the Final Appraisal Determination.

- Manufacturer/sponsors
- Professional/specialist and patient/carer groups
- Commentator organisations (without the right of appeal)

In addition, individuals selected from clinical expert and patient advocate nominations from the professional/specialist and patient/carer groups were also invited to comment on the ACD.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of evidence supporting the recommendations is not specifically stated.

The Appraisal Committee considered clinical and cost-effectiveness evidence submitted by the manufacturer of rivaroxaban and a review of this submission by the Evidence Review Group (ERG). The main clinical effectiveness evidence came from an international, multicentre, randomised controlled trial (RCT). For cost-effectiveness, the Appraisal Committee considered the manufacturer's economic model.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate use of rivaroxaban for preventing adverse outcomes after acute management of acute coronary syndrome (ACS)

Potential Harms

The summary of product characteristics includes the following adverse reactions for rivaroxaban: anaemia, dizziness, headache, fainting, bleeding events, tachycardia (rapid heartbeat), low blood pressure, haematoma, stomach pain, dyspepsia (heartburn), nausea, constipation, diarrhoea, vomiting, pruritus (itching), rash, bruising, pain in the extremities, fever, and swelling, especially of the ankles and feet.

For full details of adverse reactions and contraindications, see the summary of product characteristics.

Contraindications

Contraindications

For full details of adverse reactions and contraindications, see the summary of product characteristics.

Qualifying Statements

Qualifying Statements

- This guidance represents the views of the National Institute for Health and Care Excellence (NICE) and was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.
- Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity and foster good relations. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties.

Implementation of the Guideline

Description of Implementation Strategy

- Section 7(6) of the National Institute for Health and Care Excellence (NICE) (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, National Health Services (NHS) England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.
- NICE has developed tools to estimate the national and local savings and costs associated with implementation.
- The Welsh Assembly Minister for Health and Social Services has issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 3 months of the guidance being published.

Implementation Tools

Mobile Device Resources

Patient Resources

Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Staying Healthy

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

National Institute for Health and Care Excellence (NICE). Rivaroxaban for preventing adverse outcomes after acute management of acute coronary syndrome. London (UK): National Institute for Health and Care Excellence (NICE); 2015 Mar. 43 p. (Technology appraisal guidance; no. 335).

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2015 Mar

Guideline Developer(s)

National Institute for Health and Care Excellence (NICE) - National Government Agency [Non-U.S.]

Source(s) of Funding

National Institute for Health and Care Excellence (NICE)

Guideline Committee

Appraisal Committee

Composition of Group That Authored the Guideline

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Financial Disclosures/Conflicts of Interest

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Electronic copies: Available from the National Institute for Health and Care Excellence (NICE) Web site .

Availability of Companion Documents

The following are available:

- Rivaroxaban for preventing adverse outcomes after acute management of acute coronary syndrome. Costing report. London (UK): National Institute for Health and Care Excellence (NICE); 2015 Mar. 11 p. (Technology appraisal guidance; no. 335). Electronic copies: Available from the National Institute for Health and Care Excellence (NICE) Web site .
- Rivaroxaban for preventing adverse outcomes after acute management of acute coronary syndrome. Costing template. London (UK): National Institute for Health and Care Excellence; 2015 Mar. (Technology appraisal guidance; no. 335). Electronic copies: Available from the NICE Web site .
- Pandor A, Pollard D, Stevenson M, Cantrell A, Chico T, Henderson R. Rivaroxaban for the prevention of adverse outcomes in patients after the acute management of acute coronary syndrome: a single technology appraisal. Sheffield (UK): University of Sheffield School of Health and Related Research (ScHARR); 2014. 126 p. Electronic copies: Available from the NICE Web site .

Patient Resources

The following is available:

- Rivaroxaban for preventing adverse outcomes after acute management of acute coronary syndrome. Information for the public. London (UK): National Institute for Health and Care Excellence (NICE); 2015 Mar. 3 p. (Technology appraisal guidance; no. 335). Electronic copies: Available from the National Institute for Health and Care Excellence (NICE) Web site. Also available for download in ePub and eBook formats from the NICE Web site. Also available in Welsh from the NICE Web site.

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC Status

This NGC summary was completed by ECRI Institute on May 11, 2015.

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